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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,329	02/15/2006	Gunter Stempfer	BPG33319ASZB	2915

72554 7590 07/14/2009

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,329	STEMPFER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14,16-22 and 24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-14, 16-22 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 5/13/09 was entered.

Amended claims 1, 3-14, 16-22 and 24-29 are pending in the present application.

Applicant's election with traverse of the species of a process in which the step of concentrating the fermentation medium is carried out prior to interruption of further processing in step (b) in the reply filed on 5/13/09 is acknowledged.

The traversal is on the ground(s) that Group I (claims 1, 2-14 and 16-22) and Group II (claims 24-29) are not independent or distinct because at least claim 1 of Group I contains an embodiment of claim 24 in Group II. Additionally, there is no serious burden for the examiner to search and examine all the claims because the claims are closely related in scope and they entail a search of essentially the same art.

This is not found persuasive for the following reasons.

Firstly, it should be noted that the restriction requirement dated 3/13/09 is **a species restriction with claims 24-29 are generic claims; and it is not a group restriction requirement with the alleged groups I and II as argued by Applicants**.

Secondly, please also note that this application is a 371 application and undue burden is not a factor in determining whether the restricted species lack unity of invention. As already set forth in the restriction requirement dated 3/13/09, since the order or sequence of a method step can be considered to be a "special technical feature"; and for this instance a process containing the step of concentrating the fermentation medium is carried out **prior to** further processing is interrupted in step b) and a process containing the step of concentrating the fermentation medium is carried

out **after** further processing is interrupted in step b), lack the same or corresponding special technical feature, and therefore the species do not relate to a single general inventive concept under PCT Rule 13.1.

However, in light of the prior art applied below the species restriction was withdrawn.

Accordingly, claims 1, 3-14, 16-22 and 24-29 are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement was withdrawn in light of Applicant's amendment filed on 12/29/08.

The prior art rejections that were set forth in the Office action dated 8/27/08 were withdrawn in light of Applicant's amendment and in favor of the new grounds of rejection set forth below.

Claim Objections

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the further limitation of "wherein the fermentation medium is concentrated prior to step b)" in claim

14 is already present at step c) in independent claim 1 from which claim 14 is dependent on.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 1, 3-7, 9-14, 17-22 and 24-29 are still rejected under 35 U.S.C. 102(b) as being anticipated by Bochner et al (US 4,680,262; IDS). ***This is a new ground of rejection.***

Bochner et al discloses a method for recovering periplasmic proteins, including heterologous eukaryotic proteins such as hGH, an interferon or a lymphokine, from transformed gram negative bacteria (see at least Summary; col. 4-6). In an exemplification, Bochner et al. teach the preparation of hGH from transformed *E. coli*, said method comprises culturing a transformant of *E. coli* W3110 tonA, phoA, phoT containing pAP-STII-hGH in 500 mL LB medium and O tetracycline at 37 ^{0}C for 8 hrs (please note that during this time period hGH is secreted into the periplasm of the transformed *E. coli* host cells); followed by seeding the 500 mL inoculum culture into the 10L fermenter containing phosphate-limiting medium at 37 ^{0}C (about 25 ^{o}C) and pH 7.5 for 36 hours (about 24 hour or about 48 hours); after which 1-butanol is added to the fermenter and steam is immediately injected into the fermenter jacket so that the

temperature of the tank rises rapidly to 50 ^{0}C, and it is held at this temperature for 10 minutes (see example 8). Then, the fermenter is rapidly cooled below 20 ^{0}C and **the cellular contents of the fermenter are harvested by centrifugation. The cell paste is first frozen at –20 ^{0}C and then transferred to –80 ^{0}C until further processing is required** (col. 5, lines 4-51). In the exemplification, Bochner et al also disclose that **prior to extraction by mixing the cell paste with 10mM Tris-HCl, pH8.0, the frozen cell paste at -80 ^{0}C is thawed overnight at 4^{0}C** (col. 12, lines 39-43).

It is noted that the as-filed specification defines the term "interrupting of the further processing" broadly. On page 7, first full paragraph states "**Said interruption of the further processing may be accomplished, for example, by maintaining, retaining, keeping or storing the fermentation harvest broth for at least one hour under appropriate conditions which ensure as far as possible the integrity of the produced polypeptide, i.e. that is not degraded or otherwise impaired in function or structure. This can be achieved, for instance, by maintaining, retaining, keeping or storing the fermentation harvest broth either in the fermentation tank (fermenter) or transferring said fermentation harvest broth into another tank or any other suitable container after collection from the fermenter. Furthermore, the fermentation harvest broth may be stirred periodically or continuously during the interruption step**".

With respect to the embodiment of claims 24-29 in which **concentrating the fermentation medium by centrifugation after further processing is interrupted in step b)**; any of the steps following fermenting the transformant bacteria in 500 mL

culture medium as discussed above (e.g., maintaining the culture in a 10L fermenter in phosphate-limiting medium at 37 ^{0}C and pH 7.5 for 36 hours; raising the temperature of the tank rises rapidly to 50 ^{0}C and held at this temperature of 10 minutes; and cooling the fermenter below 20 ^{0}C) is considered to be an interrupting step (please also refer to the broad definition of the present application as already stated above) prior to extraction .

With respect to claims 1, 3-7, 9-14, 17-22 and the embodiment of claims 24-27 and 29 in which **concentrating the fermentation medium by centrifugation prior to further processing is interrupted in step b)**; the step where the cell paste is first frozen at –20 ^{0}C and then transferred to –80 ^{0}C until further processing is required and/or the step of thawing the frozen cell paste at -80 ^{0}C is thawed overnight at 4^{0}C prior to extraction is considered to be an interrupting step prior to extraction. It is noted that Bochner et al teach specifically that **the cell paste typically contains residual quantities of the fermented culture medium** (col. 5, lines 37-42). Additionally **overnight encompasses a time period of about 12 hours or more**.

Accordingly, the teachings of Bochner et al meet every limitation of the instant broad claims. Therefore, the reference anticipates the instant claims as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 24 (an embodiment) and 28 (an embodiment) are rejected under 35 U.S.C. 103(a) as being unpatentable over Bochner et al (US 4,680,262; IDS) in view of Ruelle, J-L (US 6,613,335). ***This is a new ground of rejection.***

Bochner et al discloses a method for recovering periplasmic proteins, including heterologous eukaryotic proteins such as hGH, an interferon or a lymphokine, from transformed gram negative bacteria (see at least Summary; col. 4-6). In an exemplification, Bochner et al. teach the preparation of hGH from transformed *E. coli*, said method comprises culturing a transformant of *E. coli* W3110 tonA, phoA, phoT containing pAP-STII-hGH in 500 mL LB medium and O tetracycline at 37 ^{0}C for 8 hrs (please note that during this time period hGH is secreted into the periplasm of the transformed *E. coli* host cells); followed by seeding the 500 mL inoculum culture into the 10L fermenter containing phosphate-limiting medium at 37 ^{0}C (about 25 °C) and pH 7.5 for 36 hours (about 24 hour or about 48 hours); after which 1-butanol is added to the fermenter and steam is immediately injected into the fermenter jacket so that the temperature of the tank rises rapidly to 50 ^{0}C, and it is held at this temperature for 10 minutes (see example 8). Then, the fermenter is rapidly cooled below 20 ^{0}C and **the cellular contents of the fermenter are harvested by centrifugation. The cell paste is first frozen at –20 ^{0}C and then transferred to –80 ^{0}C until further processing is required** (col. 5, lines 4-51). In the exemplification, Bochner et al also disclose that **prior to extraction by mixing the cell paste with 10mM Tris-HCl, pH8.0, the frozen cell paste at -80 ^{0}C is thawed overnight at 4^{0}C** (col. 12, lines 39-43). With respect to

claims 1, 8 and the embodiment of claims 24 and 28 in which **concentrating the fermentation medium by centrifugation prior to further processing is interrupted in step b)**; the step where the cell paste is first frozen at –20 ^{0}C and then transferred to –80 ^{0}C until further processing is required and/or the step of thawing the frozen cell paste at -80 ^{0}C is thawed overnight at 4^{0}C prior to extraction is considered to be an interrupting step prior to extraction. It is noted that Bochner et al teach specifically that **the cell paste typically contains residual quantities of the fermented culture medium** (col. 5, lines 37-42). Additionally **overnight encompasses a time period of about 12 hours or more**.

However, the Bochner et al do not teach specifically the frozen cell paste at -80 ^{0}C could be thawed at a temperature of from about 10^{0}C to about 25^{0}C.

At the effective filing date of the present application, Ruelle J-L already taught that **frozen cell paste can be thawed at room temperature which is about 25^{0}C or less, for 60 minutes prior to extraction by resuspending the thawed cell paste in phosphate buffer for homogenization** (see at least example 4, particularly col. 33, lines 21-40 and col. 34, lines 19-20).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Bochner et al by also thawing the frozen cell paste at room temperature in light of the teachings of Ruelle J-L as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Ruelle J-L already taught that frozen cell paste could also be thawed at room temperature prior to extraction.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Bochner et al and Ruelle J-L, coupled with a high level of skill of an ordinary skilled artisan in the relevant art. Therefore, the modified method resulting from the combined teachings of Bochner et al and Ruelle J-L is indistinguishable from the method as broadly claimed.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bochner et al (US 4,680,262; IDS) in view of Wisniewski, R (US 6,337,205). ***This is a new ground of rejection.***

The teachings of Bochner et al were already presented above. **However, Bochner et al do not teach explicitly that the cell paste is frozen in a fermenter**.

At the effective filing date of the present application, Wisniewski already disclosed the use of **cryopreservation vials of various shapes and sizes for storing various products including proteins, DNA, RNA, biological cells such as bacteria, fungi, yeasts, mammalian cells at temperatures from about -1^{0}C to about -200^{0}C** (see at least Summary of the Invention, particularly col. 2, lines 61-67; Figures 2-3, 7-10; col. 12, lines 11-14; and col. 13, lines 33-49).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Bochner et al by also freezing and storing the cell paste at –80 ^{0}C

in anyone of the cryopreservation vials taught by Wisniewski as discussed above until further processing. The cryopreservation vials, including those in the shape of a tissue culture flask such as those shown in Figure 3C, Figure 7A and Figure 8B, can also be used as a fermentation flask/vial, and therefore they are indistinguishable from a fermenter.

An ordinary skilled artisan would have been motivated to carry out the above modification because Wisniewski already disclosed the use of cryopreservation vials of various shapes and sizes for storing various products including proteins, DNA, RNA, biological cells such as bacteria, fungi, yeasts, mammalian cells at temperatures from about -1^{0}C to about -200^{0}C.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Bochner et al and Wisniewski, coupled with a high level of skill of an ordinary skilled artisan in the relevant art. Therefore, the modified method resulting from the combined teachings of Bochner et al and Wisniewski is indistinguishable from the method as broadly claimed.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Pluckthun et al (US 7,033,798) teach that **an overnight incubation is a 20h-incubation period** (see at least col. 8, line 63; col. 11, line 7; col. 12, line 9).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
Primary Examiner, Art Unit 1633